Predicting Functional Gains in a Stroke Trial

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Background and Purpose—A number of therapies in development for patients with central nervous system injury aim to reduce disability by improving function of surviving brain elements rather than by salvaging tissue. The current study tested the hypothesis that, after adjusting for a number of clinical assessments, a measure of brain function at baseline would improve prediction of behavioral gains after treatment.

Methods—Twenty-four patients with chronic stroke underwent baseline clinical and functional MRI assessments, received 6 weeks of rehabilitation therapy with or without investigational motor cortex stimulation, and then had repeat assessments. Thirteen baseline clinical/radiological measures were evaluated for ability to predict subsequent trial-related gains.

Results—Across all patients, bivariate analyses found that greater trial-related functional gains were predicted by (1) smaller infarct volume, (2) greater baseline clinical status, and (3) lower degree of activation in stroke-affected motor cortex on baseline functional MRI. When these 3 variables were further assessed using multivariate linear regression modeling, only lower motor cortex activation and greater clinical status at baseline remained significant predictors. Note that lower baseline motor cortex activation was also associated with larger increases in motor cortex activation after treatment.

Conclusions—Lower motor cortex activity at baseline predicted greater behavioral gains after therapy, even after controlling for a number of clinical assessments. The boosts in cortical activity that paralleled behavioral gains suggest that in some patients, low baseline cortical activity represents underuse of surviving cortical resources. A measure of brain function might be important for optimal clinical decision-making in the context of a restorative intervention. **(*Stroke*. 2007;38:2108-2114.)**

Key Words: functional MRI ■ plasticity ■ recovery ■ stroke

Stroke remains the leading cause of adult disability in the United States and many other countries[1] with motor deficits being among the most common contributors to this.[2] Advances in acute stroke therapy have identified interventions that can reduce infarct size and improve patient outcomes.[3] In parallel, a range of therapeutic approaches[4–6] is under investigation targeting the time period beyond the initial poststroke hours. These restorative interventions aim to improve outcome not by salvaging injured tissue, but rather by promoting repair and favorably modifying function within surviving brain areas.

Clinical stroke trials aim to enroll those most likely to respond to therapy. Predicting the population that will have optimal response to therapy is a complex challenge.[7–10] Entry criteria often approach this goal by using clinical measures such as time after injury, age, and severity of baseline behavioral deficit. Such measures are high in accessibility but often only approximate the physiological state of the tissue target.[11] A more direct measure of the brain biological target would likely improve the ability to selectively enroll patients with high likelihood of therapeutic benefit, particularly because a wide range of brain events and behavioral strategies can produce the same behavioral phenotype. This approach has received increased attention in the acute stroke setting,[3,12,13] in which measurement of brain injury and perfusion have proven instructive. In the setting of chronic stroke,

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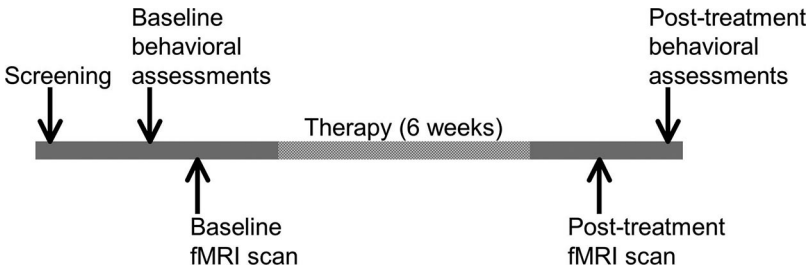

Figure 1. Study timeline.

when an intervention is restorative, a measure of functional neuroimaging might have similar use for at least 2 reasons. First, for an intervention that improves behavior by changing brain function, a baseline measure of brain function within the behavioral system of interest might be informative as to likelihood of achieving gains in the behavior of interest. Second, in some settings,[14–17] human brain mapping provides insights into neurologically relevant brain events that are not available from behavioral examination or anatomical imaging.

The current study examined this possibility by addressing the hypothesis that after adjusting for other baseline variables, a lower degree of activation in the motor cortex at baseline predicts both larger motor gains as well as larger increases in motor cortex activity from subsequent therapy. Degree of motor cortex activation refers to the change in functional MRI (fMRI) signal between rest and motor task performance. As a corollary, other measures of motor cortex activation, including site and volume, were also analyzed. These hypotheses were motivated in part by prior observations that therapies that improve motor function in the chronic stroke setting have been associated with an increase in several measures of motor cortex activation.[18] Other predictive baseline variables evaluated in the current study along with fMRI measures of motor cortex function included established predictors of spontaneous behavioral recovery after stroke[7,8] such as subject age, time poststroke, baseline deficits, and infarct volume. Degree of motor cortex activation was measured through an fMRI scan during performance of a motor task by the affected arm obtained before therapy initiation. Prediction of behavioral gains was evaluated in the context of a clinical trial of 6 weeks of rehabilitation therapy with versus without simultaneous motor cortex stimulation.

Methods

Subjects and Clinical Trial Design

At each of 7 US medical centers, patients with a chronic ischemic stroke and moderate arm paresis were evaluated for enrollment in an unblind, prospective, randomized study to evaluate subthreshold motor cortex electrical stimulation arm motor deficits. Enrollment consisted of consent in accordance with local Institutional Review Boards, screening, and baseline clinical and MRI assessments, including arm motor Fugl-Meyer (FM) score. The arm motor FM score[19,20] evaluates 33 features of arm motor behavior and was a study primary outcome measure. Scores on the arm motor FM score range from 0 to 66 with higher scores representing superior function. Patients meeting entry criteria and having an interpretable fMRI scan showing ipsilesional motor cortex activation and then received 6 weeks of therapy with randomization to either no cortical stimulation or concurrent cortical stimulation from an implanted investigational cortical stimulation device system (Northstar Neuroscience). The MRI scan was repeated within 2 weeks and the arm motor FM score reassessed within 4 weeks after completing rehabilitation therapy.

Enrollees were required to have ischemic stroke that was at least 4 months previously; arm motor FM score between 20 to 50 points; active wrist extension of at least 5°; age ≥21 years; no history of seizure; and no substantial neglect, depression, or sensory deficit.[21] Any patient started in the prior 2 months on a medication that could potentially confound a study of stroke recovery such as amphetamine, antiepileptics, anxiolytics, or antidepressants was excluded. A total of 38 patients were enrolled across 7 centers to obtain 24 eligible patients at 5 centers.

The study timeline (Figure 1) started with baseline assessments, which included demographic data, fMRI scanning, and arm motor FM score. Participants with scans free of artifact were then randomized as described previously.

All patients then received 6 weeks of rehabilitation therapy that targeted arm motor function, especially distally. The therapy program consisted of task-oriented training of goal-directed movements. Strategies for reaching, grasping, lifting, and manipulating objects were emphasized as were self-care and activities of daily living. Proximal arm strengthening and range of motion were also incorporated. The program included 4 weeks (5 days per week) of this therapy in all cases. In the first 7 subjects, this was followed by 2 additional weeks (3 days/weeks) of this program therapy, and for the remainder, this was preceded by 2 weeks of rehabilitation preconditioning. Each session lasted approximately 2.5 hours.

For patients randomized to therapy plus cortical stimulation, the most significantly activated voxel on the posterior half of the precentral gyrus of the stroke-affected hemisphere was identified and used to guide placement of the epidural electrode. This electrode was connected to a stimulator that was switched on during therapy. The electrode was removed on completion of the 6 weeks of rehabilitation therapy.

Functional MRI Scanning

At each site, before therapy, each patient underwent fMRI that alternated 20 seconds rest with 20 seconds of motor task performed by the paretic hand. These rest/task cycles were repeated for a total of 300 brain volumes. The task performed was index finger tapping when possible, wrist extension, or squeezing (gently on a tennis ball) at 0.25 Hz in all cases. Before scanning, each patient was trained to move approximately 5° entrained by an auditory metronome.

Each site imaged with standardized parameters: time to repetition=2000 ms, echo time=50 ms, in-plane resolution=3.75×3.75 mm, and field of view that included cerebral vertex to Sylvian fissure through 5-mm axial slices with interslice gap=0 mm. A volumetric T1-weighted anatomical image (slice thickness 1 to 2 mm) was also acquired during this session. At 3 sites, data were acquired with a 3.0-T Siemens scanner; at one site, a 3.0-T General Electric scanner; and at one site, a General Electric 1.5-T scanner. Each subject returned to the same scanner for repeat MRI with the same activation task at the same movement rate approximately 2 weeks after the end of therapy.

Image Analysis

Images were processed at each site using an automated script run with MEDx software (Sensor Systems). Motion correction and in-plane spatial smoothing (6-mm full-width half-maximum) were followed by linear detrending and generation of Z-maps contrasting

blocks of movement with rest. At one of the author's laboratories (S.C.C.), infarct volume was determined from the volumetric anatomical images using semiautomated methods, which consisted of using thresholds to estimate an infarct mask and then refining this by hand to achieve final values. Motor cortex activation volume was determined by measuring the volume of the largest activation cluster on the posterior precentral gyrus of the stroke-affected hemisphere thresholded at $Z > 3$. Motor cortex activation site was determined by identifying the Talairach coordinates (x, y, z) for the most significantly activated voxel within this cluster. Degree of motor cortex activation represents percent change in MRI signal between rest and movement and was measured as the mean across all voxels in 5 motor cortex regions of interest on each subject's activation map. Note that even when an ipsilesional motor cortex activation cluster is clearly present, mean degree of activation can be positive or negative because of the large number of voxels in a region of interest. The main region of interest was the hand area of ipsilesional primary motor cortex, which was defined in 3 different ways. The first method, which was used in the primary statistical analyses, used a region of interest weighted according to meta-analysis of prior imaging studies (http://hendrix.imm.dtu.dk/services/jerne/ninf/voi.html) as represented in Talairach stereotaxic space. Two secondary analyses defined hand area differently to test the robustness of degree of activation in ipsilesional primary motor cortex. One approach used a 12-mm sphere centered about the middle of this same region of interest with all voxels weighted the same. A third approach used a 12-mm sphere centered about the motor cortex activation site as defined for each individual subject. The other 4 regions were the contralesional primary motor cortex using the same meta-analysis region as previously mentioned but in the opposite hemisphere; a 12-mm sphere centered around premotor cortex coordinates in each hemisphere, also determined from the previously mentioned url; and a 12-mm sphere centered around the supplementary area as defined by the previously mentioned url.

Statistics

The primary outcome measure that was evaluated, change in arm motor FM score, was determined from the first pretherapy assessment to 4 weeks after the end of rehabilitation treatment. Thirteen baseline predictive variables were evaluated, including established[7,8] predictors of outcome after stroke (baseline clinical status measured here as arm motor FM score, age, time poststroke, and infarct volume) and measures of brain activation related to the study hypothesis (fMRI motor cortex activation volume; activation site with x-, y-, and z-coordinates treated separately; and degree of activation in each of the 5 motor cortices). Attempts were made to transform nonnormally distributed variables whenever possible; this could be accomplished for infarct volume (through natural log transform) and for activation volume (through square root transform). For comparison of baseline measurements, a 2-sample *t* test was used for normally distributed measurements, which were all except activation site x, y, and z plus degree of activation; these 4 were both nonnormally distributed and therefore evaluated with the Wilcoxon rank test.

Bivariate analysis was performed to evaluate the linear relationship between each potential predictive variable, measured at baseline, and the outcome variable using Pearson correlation for normally distributed measurements and Spearman rank ordered correlation for nonnormally distributed measurements. Next, a multivariate linear regression model using forward stepwise selection (probability to remain in the model of $P \leq 0.15$) determined which baseline predictive variables have a significant effect on predicting the change in arm motor FM score. The residuals of the regression model were examined for normality assumption. Partial correlation coefficients were also determined. All analyses were done using SAS 9 and JMP-5 with a significance level of 0.05 for 2-sided testing.

Results

A total of 24 patients met all entry criteria and were randomized, 15 male and 9 female, 21 right-handed and 3 left-handed, with stroke affecting the dominant side in 13 and nondominant in 11. Stroke topography was subcortical in 12, cortical in 3, both in 8, and pontine in one. The motor task during fMRI was index finger tapping for 4, wrist extension for 17, and squeezing for 3. Investigator assessment of motor task performance during fMRI indicated 21 subjects with accurate performance and 3 subjects with reduced but present movements.

TABLE 1. Predictive Variables: Distribution and Correlation With Outcome Measure

Predictive Variable	Mean±SD	Correlation With Change in Arm Motor FM Score	*P* Value for Correlation
Baseline arm FM motor score	32.4±8.3	0.47	0.02
Age, years	57.6±13.9	−0.16	0.47
Time poststroke, months	33.1±23.3	0.14	0.51
Stroke volume, cc	54.0±143	−0.48	0.02
Activation volume, mm^3	9176±8663	0.03	0.89
Activation location—x	31.5±5.7	−0.08	0.73
Activation location—y	−25.7±8.1	0.12	0.57
Activation location—z	50.7±5.5	0.006	0.98
Degree of activation			
Ipsilesional motor cortex	0.47±0.59	−0.45	0.03
Contralesional motor cortex	0.45±0.60	−0.21	0.33
Ipsilesional premotor cortex	0.49±0.47	0.02	0.93
Contralesional premotor cortex	0.35±0.34	−0.13	0.55
Supplementary motor area	0.58±0.49	−0.26	0.21

For each of the 13 predictive variables, the distribution (column 2) and bivariate correlation with the outcome measure (columns 3 to 4) are presented. *P* values are not corrected for multiple comparisons. Data are for all 24 patients.

Baseline values for predictive variables are presented in Table 1. None was significantly different ($P=0.14$ to $P=0.91$) between the 2 treatment arms. The outcome variable, change in arm motor FM scores from baseline to 4 weeks after the end of therapy, showed an overall increase of 4.1±4.8 (mean±SD; range, −3 to 17) points with patients receiving rehabilitation therapy+stimulation improving 5.8±4.7 points and patients receiving rehabilitation therapy alone improving 2.5±4.5 points. These arm motor FM changes differ slightly from those reported elsewhere, because the current analysis used a single baseline measure for all predictive variables, including arm motor FM scores, whereas the other analysis used the average of 2 baseline arm motor FM scores (Huang M, unpublished data). Direct comparison of the 2 groups by *t* test did not disclose a significant difference in gains ($P=0.097$), but, as described elsewhere (Huang M, unpublished data), repeated-measures analysis of variance modeling using the GENMOD procedure in SAS found significantly greater gains with stimulation during the entire follow-up period from 4 to 24 weeks posttherapy ($P=0.042$). Of the 24 patients, 18 showed a gain in arm motor FM score, 11 of 12 in the rehabilitation+stimulation

TABLE 2. Multivariate Analysis

Parameter	Estimate	95% CI	$P>\|t\|$
Baseline arm motor FM score	0.24	0.04–0.044	0.024
Degree of activation in ipsilesional primary motor cortex	−3.54	−6.26–−0.82	0.019

The overall model $r^2=0.40$. Residuals of the multivariate model were normally distributed.

group, and 7 of 12 in the rehabilitation therapy alone group.

Bivariate analyses (Table 1) for the 13 predictive variables found that 3 had a significant relationship with the change in arm motor FM score ($0.01 < P < 0.05$). These 3 were retained in the stepwise multivariate linear regression model.

The multivariate model (Table 2; Figure 2A, B) found that 2 of the 3 variables evaluated had significant predictive value. Specifically, a lower degree of activation in ipsilesional primary motor cortex and higher arm motor FM score predicted a higher change in arm motor FM score during the study. That each of these 2 factors contributed to the predictive ability of the model is supported by the partial correlation coefficients that each had with change in arm motor FM score ($r=-0.48$ for degree of activation in ipsilesional primary motor cortex and $r=0.46$ for baseline arm motor FM score). Degree of ipsilesional primary motor cortex activation was a solid predictor, because when either of the secondary definitions of this measure was used instead, degree of ipsilesional primary motor cortex activation became the only significant variable surviving the model.

Other variables of potential interest did not influence model results. Each of the following variables of interest, when added to the model, was not significant and did not change model results: treatment arm assignment, side of

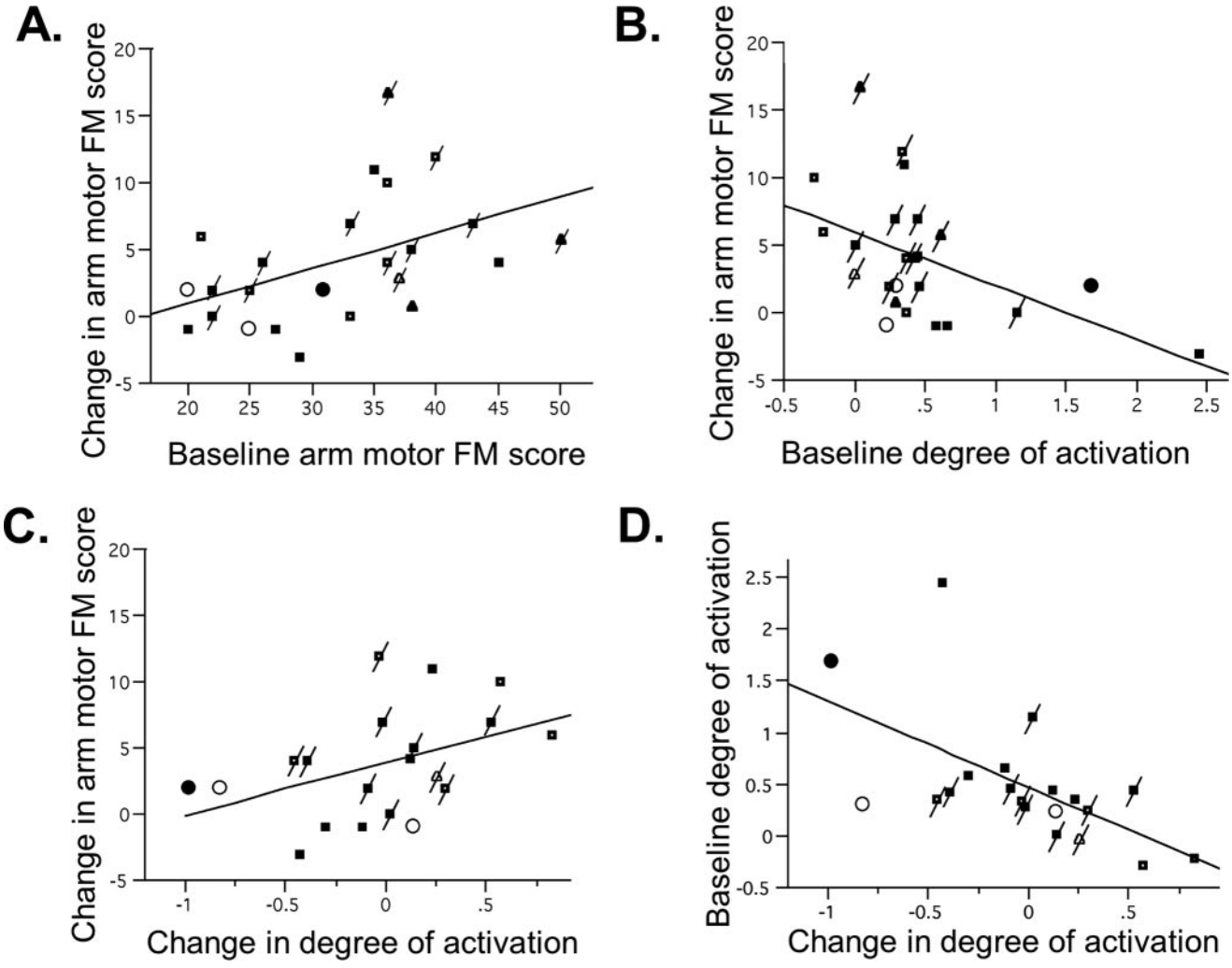

Figure 2. Three measures that are related to behavioral gains during clinical trial participation. A measure of baseline motor status (arm motor FM score, A) and of baseline brain function (degree of activation in ipsilesional primary motor cortex, measured from fMRI brain mapping, B) each predict behavioral gains from subsequent therapy. These behavioral gains were paralleled by an increase in degree of ipsilesional primary motor cortex activation on fMRI scanning (C). Furthermore, those subjects with the smallest degree of ipsilesional primary motor cortex activation at baseline had the biggest changes in this measure after treatment (D). Thus, those subjects with the smallest degree of activation at baseline had the biggest clinical gains in parallel with the largest increases in cortical activity over time. Squares indicate wrist extension used as the motor task during fMRI; circles, grasping; and rectangles, index finger tapping. Solid symbols are data acquired at 3-T MRI; hollow symbols, at 1.5 T. A slash indicates subjects in the therapy+stimulation group; no slash, rehabilitation therapy alone group.

stroke, topography of stroke, enrollment site, and fMRI activation task. Degree of ipsilesional primary motor cortex activation ($P<0.005$), but not volume or site, differed significantly in relation to MRI field strength, but the level of motor deficits were evenly distributed across the 2 different scanner field strengths ($P>0.4$). Degree of activation in ipsilesional primary motor cortex did not differ across fMRI motor tasks. Restricting data analysis to only the 17 of 24 subjects who performed wrist extension during fMRI had no effect on the multivariate analysis (Table 2) with trivial changes in the estimate and no change in the probability values.

On repeat fMRI scanning (n=20), the change in degree of activation over time within the ipsilesional primary motor cortex correlated with change in arm motor FM score ($r=0.46$, $P<0.05$; Figure 2C). Also, the change in degree of activation over time within the ipsilesional primary motor cortex was inversely related to the degree of ipsilesional primary motor cortex activation at baseline ($r=-0.59$, $P<0.007$; Figure 2D). Overall, there was no significant change over time in degree of activation within ipsilesional primary motor cortex, ie, the average degree of activation at baseline was not significantly different than the average degree of activation posttherapy (0.47 ± 0.59 versus 0.47 ± 0.52, $P>0.9$). Also, the degree of ipsilesional primary motor cortex activation was not significantly different between the 2 treatment groups at either time point. Note too that the degree of ipsilesional primary motor cortex activation at either of the 2 fMRI scans did not correlate with baseline arm motor FM score ($P>0.5$). Of the 20 subjects able to undergo repeat fMRI scanning, 18 performed the same motor task at both fMRI scans, whereas the task was different in 2; removal of the latter 2 had no effect on results.

The presence of carotid disease was examined because of its potential effects on fMRI results. Seventy percent or greater internal carotid artery stenosis was present on the side of the infarct in 4 patients. The 4 patients with internal carotid artery disease on the side of the infarct, as compared with the 20 who did not, had larger infarct volumes (226 ± 307 versus 20 ± 47 mL, $P<0.05$) and greater deficits (baseline arm motor FM score (23 ± 4 versus 34 ± 8, $P<0.005$). However, carotid narrowing was not associated with differences in any of the other predictive variables, including the fMRI measures.

Discussion

The current study found that degree of behavioral improvement over 6 weeks of participation in this restorative stroke study was predicted by 2 baseline measures, arm motor function and degree of ipsilesional primary motor cortex activation during affected hand movement. To our knowledge, this is the first demonstration that predicting treatment-related gains in a clinical trial setting can be improved by measuring baseline brain function. Predicting behavioral gains in a restorative stroke trial might therefore be most accurately achieved by including a baseline measure of brain function along with clinical assessments.

The degree of ipsilesional primary motor cortex activation during affected hand movement was a significant predictor of behavioral gains during the trial (Table 2; Figure 2). Subjects with smaller baseline cortical activity had larger behavioral gains (Figure 2B) and larger increases in cortical activity (Figure 2D) after therapy, whereas subjects with larger baseline cortical activity had poorer behavioral gains with less boosts in cortical activity over time. One interpretation of this constellation of findings is that subjects with the highest level of baseline cortical activity were already operating in a state of maximum output with no reserve remaining to boost either cortical activity or behavioral output in response to treatment. Subjects with lower baseline primary motor cortex activity were a mixed population. Some were able to increase activity in parallel with gains in behavioral status, possibly indicating learned nonuse[22] of an available and modifiable substrate at baseline. Others were in a different state and not able to increase either behavior or cortical activity. Future studies can address a corollary hypothesis that the latter subgroup can be prospectively distinguished on the basis of reduced neurophysiological[23,24] and/or radiological[25] measures of corticospinal tract integrity.

Degree of ipsilesional primary motor cortex activation predicted trial-related gains, but volume and site of activation, which often change after stroke,[26] did not (Table 1). One possible reason for this constellation of findings is that degree of activation might have the most direct relationship to the neuronal events most important to achieving treatment-related behavioral gains given its relationship to neuronal and synaptic activity.[27–30] Degree of activation had a predictive value in the ipsilesional primary motor cortex, but not within the secondary and contralesional motor regions examined, attesting to the critical importance of the primary motor cortex in the genesis of voluntary motor behavior.

The current findings were derived by combining subjects in the 2 treatment groups. Whereas the repeated-measures modeling used to analyze the full clinical trial found an outcome difference among the 2 treatment groups (Huang M, unpublished data), the difference between treatment groups in a measure of clinical status at one time point posttherapy did not reach significance, and a factor representing treatment arm assignment was not significant when added to the model and did not change model results.

Several studies have examined the effect of a restorative intervention on brain function in humans.[31–39] In general, interventions that improve motor behavior in the setting of chronic stroke are associated with parallel increases in activity of sensorimotor cortices either ipsilesionally or bilaterally.[18] A smaller number of studies have used assessment of brain function to predict response to a restorative intervention.[40–43] For example, Koski et al,[43] using transcranial magnetic stimulation, and Dong et al,[41] using fMRI, have found that changes in brain function early into therapy anticipate final behavioral gains. The current study extends these efforts in 2 main ways. First, prediction was assessed from a single baseline assessment. Second, multivariate linear regression modeling was used to confirm that an assessment of brain function has predictive value after controlling for other baseline measures, many of which are known to predict outcome in spontaneous stroke recovery.

Baseline clinical status was a second measure independently associated with greater gains from therapy. Such clinical measures are known to have predictive value for

response to rehabilitation therapy,[7–9] but alone do not completely predict treatment-related gains. The current results suggest that adding a measure of brain function to clinical assessments improves ability to predict behavioral gains after restorative therapy. The current study used fMRI for this measure, but a range of brain mapping methods, including some easier to use in the study of patients with stroke,[23,44–46] might have similar predictive value.

The multivariate model (Table 2) accounted for 40% of variance in the outcome measure. Other sources of variance included lesion side, MRI field strength, therapeutic intervention, fMRI activation task, as well as intersubject differences in the many other variables that modify brain function after stroke.[47] These might have also contributed to the limited relationship observed between arm motor FM score and fMRI measures at baseline, although enrollment of patients with deficits spanning a relatively wide range might also underlie this finding. However, despite these sources of variability, degree of activation within the ipsilesional motor cortex at baseline was one of the primary predictors of therapy-related behavioral gains, remaining significant when several different approaches were used.

In conclusion, both clinical assessments and a measure of brain function are useful to best predict behavioral gains from restorative therapies. Future studies might evaluate the current findings in the setting of other restorative therapies or examine the use of a baseline measure of brain function to serve as an entry criterion or to guide dose of a restorative intervention. As restorative therapeutic approaches[4] continue to advance through clinical trials, measures of brain function will likely prove useful as an adjunct to clinical assessments.

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Disclosures

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